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Time to RethinQ PROSPECT?

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This commentary refers to 'Characteristics of heart failure patients associated with good and poor response to cardiac resynchronization therapy: a PROSPECT (Predictors of Response to CRT) subanalysis'†, by R.J. van Bommel *et al.*, on page 2470

Cardiac resynchronization therapy (CRT) is the most successful therapy in treating chronic heart failure patients since the introduction of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and spironolactone into the therapeutic regimen. Recent studies (REVERSE, MADIT-CRT) will probably expand the indication for CRT to mild and asymptomatic heart failure patients [New York Heart Association (NYHA) functional class I and II], an enormous task for physicians and healthcare providers. CRT with current indications appears to improve the clinical status in ~70% of patients. This compares well with the effects of treatments of chronic and life-threatening diseases in other medical fields.

However, indications for CRT are currently based to a large degree on QRS width in an attempt to detect mechanical dyssynchrony under the assumption that correction of dyssynchrony is the main mechanism of action. The idea behind the original Predictors of Response to CRT (PROSPECT) study was to identify in a non-randomized observational design the predictive value of predefined echocardiographic parameters of mechanical dyssynchrony with regard to clinical and left ventricular mechanical outcome after CRT.[1] Twelve previously published parameters of dyssynchrony, both conventional and tissue Doppler-based methods, had finally been used in 426 CRT patients at 53 centres. Considering the intended purpose of the PROSPECT study, the overall results were not encouraging, with no single echocardiographic dyssynchrony parameter being highly predictive of the CRT response at follow-up. There seemed to be no 'holy grail' of echocardiographic dyssynchrony parameter which by itself could be used for decision making regarding CRT.

Is this the end of the 'mechanical dyssynchrony' hypothesis? Is echocardiography useless in predicting CRT respsonse despite numerous single-centre studies showing high sensitivity and specificity? Immediately after publication of the PROSPECT results, numerous concerns regarding the design of the study and the way in which it was conducted were raised, especially regarding patient selection as well as echocardiographic assessment. Concerning patient selection, 20.2% had a left ventricular ejection fraction (LVEF) >35%, and 37.8% had a left ventricular end-diastolic diameter (LVEDD) <65 mm, which ultimately raised the question of how reverse remodelling could be achieved in a non-dilated heart.[2] This, together with a substantial interobserver variability and large percentage of non-assessable echocardiographic studies, indicated a lack of standardized data acquisition and analysis. In addition, tissue Doppler imaging (TDI) data were obtained using echo machines from thee different ultrasound providers without standardization of frame rates, and three different software programs were used for offline data analysis. Furthermore, there was no information on left ventricular lead placement and percentage biventricular pacing. Taken together, important technical limitations as well as suboptimal patient selection may importantly confound and limit the interpretation of the initial PROSPECT study results.

Van Bommel *et al.* have performed a subgroup analysis of 286 of the total of 498 patients which had initially been enrolled into PROSPECT;[3] 426 of those had been originally analysed in the main PROSPECT study after 31 early exits and the exclusion of 41 patients with narrow QRS (<130 ms). Eventually, this substudy analysed 57% of the total PROSPECT population, further excluding 15 patients who died, 18 patients who had been lost for the 6-month follow-up visit, and 44 patients with incomplete data from the 6-month follow-up visit, thus ending up with 286 patients with a complete data set and paired left ventricular end-systolic volume (LVESV) measurements. Overall, this represents quite a substantial reduction compared with the 498 originally enrolled patients.

In order to dissect the response to CRT, the authors grouped patients according to both a combined clinical and a pure echocardiographic response. Echocardiographically, subgroups were formed consisting of so-called 'super-responders' with a reduction of >30% in LVESV; 'responders' with a 15–29% reduction in LVSEV; 'non-responders' without evidence of reverse remodelling and reduction of LVESV between 0 and 14%; and 'negative responders' with echocardiographic signs of disease progression despite CRT with an increase in LVESV after 6 months. Clinically, they

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grouped their patients according to a combined clinical composite score (CCS) measured 6 months after implantation. A positive clinical response was defined as the patient surviving and not being hospitalized for heart failure, demonstrating improvement in NYHA class at the last observation carried forward, or having moderate or marked improvement in patient global assessment score at the last observation carried forward. Finally, using both clinical and echocardiographic data, they formed three subgroups according to clinical and/or echocardiographic response: (1) +/+ responders (improved CCS and a reduction in LVESV >15%); (2) +/− responders (improved CCS or a reduction in LVESV >15%); and (3) −/− responders (no improvement in CCS and no reduction in LVESV >15%).

When looking at the pure mechanistic outcome, i.e. echocardiographic parameters of left ventricular structure and function, of the 286 studied patients, 56.3% had significant evidence of reverse remodelling. It is well known that some patients have an extraordinarily good response to CRT (the so-called 'super-responders') with a >30% reduction of LVESV. Compared with patients who deteriorated, the 'negative responders', it is not surprising that significantly more patients had a non-ischaemic aetiology (resulting in less scar burden and more viable myocardium for reverse remodelling) in the 'super-responder' subgroup. These patients also less commonly had a history of ventricular tachycardia, which might be explained by the underlying disease aetiology and the disease state, with significantly fewer patients in NYHA class IV in this subgroup. Interestingly, at baseline 'super-responders' were significantly more dyssynchronous than the 'negative responders', as evidenced by a larger interventricular mechanical delay (IVMD; 55 ± 35 ms vs. 25 ± 39 ms, $P = 0.0002$) and septal to lateral delay on tissue Doppler (68 ± 44 ms vs. $44 \pm$ ms; $P = 0.0022$). This observation is in line with a recent report in the CARE-HF trial, showing that patients with wide QRS and and IVMD >49 ms treated with CRT showed superior survival.[4] Indeed, pathophysiologically, IVMD reflects left to right heart interaction and is useful only in patients with a broad QRS complex; conversely, IVMD is virtually absent in patients with a narrow QRS complex.[5] Importantly, both echocardiographic parameters can be measured relatively easily, and IVMD is one of the most robust parameters with respect to interobserver variability. Hence, the findings of van Bommel and colleagues[3] support for the first time in a multicentre environment with >53 centres the concept that we are in fact treating mechanical dyssynchrony with CRT.

When looking at the CCS after 6 months, a greater percentage of patients showed signs of clinical benefit than evidence of reverse remodelling. In fact, 209 out of 286 patients (73%) had a positive CCS, while only 114 patients showed a clinical response without significant change in LVSEV (40%). This is remarkable but not very surprising. CRT can stabilize patients with advanced heart failure, i.e. 'non-progressors'; however, these patients do not necessarily have signs of reverse remodelling, possibly due to an already too advanced disease and/or scar burden. Yet, clinical improvement is of great interest for the patient and should therefore importantly be counted as therapeutic success. This is why withholding CRT from a patient with a QRS >130 ms just because of a lack of echocardiographic signs of dyssynchrony does not seem to be justified, merely based on a slightly inferior prediction of reverse remodelling.

Taken together, the current substudy of PROSPECT by van Bommel *et al.*[3] adds important evidence to the current literature. However, even after this careful examination of the available data within the PROSPECT cohort and a positive correlation between baseline echocardiographic dyssynchrony and reverse remodelling, the presented evidence does not appear to be strong enough to change current clinical practice and exclude patients fulfilling current guidelines for CRT simply based on lack of dyssynchrony on echocardiography. Other limitations, which were equally inherent to the original PROSPECT trial, are also problematic for the current substudy. Importantly, the short-term follow up of only 6 months is far too little to assess the entire effect of CRT on remodelling and, eventually, morbidity and mortality. Indeed, had CARE-HF been stopped after 6 months, no significant effect on morbidity and mortality would have been observed; furthermore, ongoing reverse remodelling was evident even after 18 months of follow-up in the CRT substudy.[6] As the authors state, the goal is to measure the impact of mechanical dyssynchrony on clinical outcome after CRT. In the end, this question can only be answered by an adequately powered randomized clinical trial. Such a trial is already underway investigating the impact on morbidity and mortality of baseline dyssynchrony in patients with symptomatic heart failure, LVEF <35% and a QRS <130 ms (Echocardiography Guided Cardiac Resynchronization Therapy, EchoCRT, NCT00683696).

Conflict of interest: none declared.

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